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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,146	10/15/2001	Shlomo Melmed	18810-81351	4097

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/978,146	Melmed et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 4, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above, claim(s) *21-24 and 33-35* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-20, 25-32, and 36* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election without traverse of group I, claims 1-20, 25-32 and 36, in Paper No. 7 is acknowledged.

2. Claims 21-24 and 33-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 7.

Claims 1-36 are pending and claims 1-20, 25-32 and 36 are under consideration.

Claim Objections

3. Claim 36 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 36 is directed to the null mutant rodent of any of claims 1 and 27-30 but the use of said rodent as an animal model for diabetes does not further limit the subject matter of parent claims.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 31 provides for the use of the null mutant rodent in the study of mammalian physiology at the cellular, tissue, and/or organismal level, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 31 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

6. Claim 32 provides for the use of null mutant rodent in the study of the role of PTTG in diabetes, hyperglycemia, hypoinsulinaemia, or hypoleltinemia, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 32 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

7. Claims 31 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "and/or" in claims 31 and 32 is vague and renders the claims indefinite. Changing the term "and/or" to "...or...or both..." would be remedial.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-20, 25-32 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of a null mutant **mouse** having null mutation on **both pituitary tumor transforming gene (PTTG) alleles** in the **germ cells** and having the **phenotypes** as disclosed in the specification, such as hyperglycemia, hypoinsulinaemia, and diabetes etc., does not reasonably provide enablement for production of any null mutant rodent having null mutation on one or both PTTG alleles other than the disclosed null mutant mice set forth above, and the use of said null mutant rodent in the study of mammalian physiology at the cellular, tissue, or organismal level, such as study of diabetes, hyperglycemia, hypoinsulinaemia, and hypoleptinemia. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-20, 25-32 and 36 are directed to a null mutant rodent comprising in its germ cells one or two artificially induced PTTG null mutation via homologous recombination with a targeting vector containing a selectable marker in an embryonic stem (ES) cell, wherein no functional PTTG protein is expressed in somatic cells or germ cells, and the use of said null mutant rodent in the study of mammalian physiology at the cellular, tissue, or organismal level, such as study of diabetes, hyperglycemia, hypoinsulinaemia, and hypoleptinemia. Claims 11-14 specify the mutated PTTG allele contains a deletion of the translation start site, a deletion of the KOZAK region, a deletion of a segment of the endogenous PTTG gene promoter region, and a deletion of the transcription start codon, respectively. Claims 25 and 26 specify the null mutant rodent is a mouse and a rat, respectively. Claims 28-30 specify the mutated PTTG allele contains a deletion of the KOZAK region, a deletion of the translation start site, and a deletion of the transcription start codon, respectively, and such deletion is obtained by mating of heterozygous male and female rodent of same species.

The specification discloses production of null mutant mice PTTG -/- having null mutation on **both PTTG alleles** in the **germ cells** and having the **phenotypes** as disclosed in the specification, such as hyperglycemia, hypoinsulinaemia, and diabetes etc., by using J1 ES cells, microinjection of selected ES cell clone into C57BL6 blastocyst to produce chimeras, and the chimeras are crossed with C57BL6 strain for the production of null mutant mice. The claims

encompass production of any null mutant rodent, including mice, squirrels, rats, hamsters, beavers, woodchucks, gophers, voles, marmots, guinea pigs, and agoutas etc., having at least one mutated PTTG allele, and the use of said null mutant rodent in the study of mammalian physiology at the cellular, tissue, or organismal level, such as study of diabetes, hyperglycemia, hypoinsulinaemia, and hypoleptinemia.

The specification fails to provide an enabling disclosure for the preparation of various null mutant rodents having at least one mutated PTTG allele containing for example, a deleted translation start site, a deleted transcription start codon, a deleted KOZAK region, or a deleted endogenous PTTG gene promoter etc., that results in non-functional PTTG protein, because it fails to provide sufficient guidance for the preparation of any heterozygous or homozygous PTTG null mutant rodent other than the PTTG -/- mice as disclosed and further because it fails to provide a suitable description of those various homozygous or heterozygous PTTG null mutant rodents. No teachings are present within the specification in regard to how one would have prepared any PTTG null mutant rodent other than the PTTG -/- mice as disclosed. The specification also fails to provide phenotypes of any heterozygous PTTG +/- null mutant rodent. The cited phenotypes in claim 27 is the resulting phenotypes of homozygous PTTG -/- null mutant mice but not the phenotypes of heterozygous PTTG +/- null mutant mice. There is no evidence of record for the resulting phenotypes of any heterozygous PTTG +/- null mutant rodent including null mutant mice.

Since the specification discloses using mouse ES cells to produce knockout mice via homologous recombination of targeting vector in the ES cells, ES cells from various rodent species are required to produce various heterozygous or homozygous PTTG null mutant rodents. However, Houdebine, 1994 (Journal of Biotechnology, Vol. 34, p. 269-287) points out that although ES cells can be used to generate transgenic animals, but this approach remains restricted to mice, ES cells from other species are not presently available (e.g. p. 279). Although rat ES cells has been discloses at the time of the invention, no transgenic knockout rat has been successfully produced via homologous recombination of targeting vector in rat ES cells. Further, Seamark, 1994 (Reprod. Fertil. Dev., Vol. 6, p. 653-657) points out that even pig's pluripotent ES cells can be created, no group has demonstrated totipotency of these cells through reinstating their genome within a germ line, and procedures for reinstating the ES cell genome into a germ line are still far from routine. Small changes in the environment the embryo is exposed to can impact on development with long-term implications on health and warefare. For example, in the mouse, brief exposure of preimplantation embryos to *in vivo* culture conditions can both result in substantial phenotypic variation and predicate the subsequent expression and penetration of some transgenes. Asynchrony between the stage of development of the embryo and tract at embryo transfer can also affect development (e.g. p. 654, 655). Therefore, the specification fails to provide adequate guidance and evidence for production of any PTTG null mutant rodent by using homologous recombination of targeting vector in ES cells other than using mouse ES cells, and

one skilled in the art at the time of the invention would not know how to produce the claimed PTTG null mutant rodents by using ES cells other than mouse ES cells.

In addition, the state of the art in the field of transgenics at the time of the invention was unpredictable. The phenotype of a transgenic knockout organism was unpredictable at the time of filing. Sigmund, June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (abstract). Wu et al., 1997 (Methods in Gene Biotechnology, CRC Press, Boca Raton, p. 339-365) pointed out that the approach of using ES cells carrying a single-copy mutation of a specific gene to generate knockout transgenic animal is time-consuming and costly to obtain homozygous or double-knockout mice, and another major concern is the potentially lethal effect of the targeted gene. In some cases, gene knockout results in early death of embryos and young animals, or morphologically and functionally abnormal offsprings such as blind and/or handicapped animals.

Further, Wolfer et al., 2002 (Trends in Neurosciences, Vol. 25, No. 7, p. 336-340) points out that flanking-gene or linkage disequilibrium problem exists in producing knockout mice having null mutation due to the use of ES cells derived from 129 INBRED mice and its crossing with C57BL6 mice, and "the phenotype resulting from a null mutation can depend on the general

genetic background of mouse strains used for this research. Thus, congenic strains carrying the same null mutation can sometimes show widely divergent phenotypes, depending on the genotype of the recipient strain" (e.g. p. 326). In view of the inherent unpredictability of the resulting phenotypes of transgenic knockout animals in general and the lack of availability of embryonic stem cells for species other than mouse and rat (no transgenic knockout rat has been successfully produced via homologous recombination of targeting vector in rat ES cells), one skilled in the art at the time of the invention would not know how to make the claimed PTTG null mutant rodents via homologous recombination in ES cells and how to use said PTTG null mutant rodent for the claimed method.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to have made and used the invention over the full scope claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.